REMARKS

Claims 1-50 are pending in the application. Claims 1, 3-30, and 32-50 stand rejected while claim 31 is listed as objected to as being dependent on a rejected claim but otherwise allowable if rewritten in independent form. Claim 1 has been amended to clarify that the word "thereby" in line 18 is being added. The word appeared as a new addition after the previous amendment but was not underlined. For the sake of formality, the instruction to add the word is being made again with the appropriate underlining.

Rejections under 35 USC §103(a)

Applicants note that all present grounds of rejection under this section of the statute appear to rely on the combination of US 4,935,342 to **Seligson** as the primary reference and US 6,060,246 to **Summerton** as the secondary with additional references cited in some cases. Applicants submit that this combination of references is defective, whether or not further modified by additional references and does not render any of the present claims obvious.

Claims 1-3, 6-12, 19-22, 30, 32-35, 42-46, and 48-50 were rejected under 35 USC § 103(a) as being unpatentable over US 4,935,342 to **Seligson** in view of US 6,060,246 to **Summerton**. This rejection is traversed. The rejection states:

> It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to include the cleavable linkers taught by Summerton in the isolation technique taught by Seligson. As taught by Seligson, prior art techniques for isolation of DNA/RNA do "not provide adequately isolated nucleic acids needed for hybridization assays in a clinical laboratory. Contaminates in the biological samples interfere with fixing DNA/RNA hybridization and detection. As a consequence, to provide useful clinical hybridization assays, there exists a need for rapid methods to obtain hybridization nucleic acids from biological samples"

and

> One of ordinary skill in the art at the time the invention was made would have recognized the benefit of enhanced and rapid isolation of nucleic acid molecules. ... Considering that Seligson is directed to obtaining hybridization nucleic acids from biological samples. The inclusion of the cleavable linker provided by Summerton provides for a more rapid release of polynucleotides which bind non-specifically to the capture component of the 'rapid pairing reagent' taught by Summerton.

Thus, the method of Seligson would be modified to include a cleavable linker connected to a target specific probe (using base pairing binding) for "enhancement of specific target sequence." Even if there is motivation in the prior art to so modify Seligson (which Applicants deny), the result of the proposed modification would not produce a method of isolating a nucleic acid using a solid phase comprising a nucleic acid binding portion for attracting and non-sequence specific binding of nucleic acids and wherein the nucleic acid binding portion includes a ternary or quaternary onium group, as called for in amended claim 1.

1. Applicants reiterate the point made previously that applying the cleavable linker methodology of Summerton to the teachings of Seligson would still result in a material and method which only results in the isolation of selected nucleic acids since a specific capture element is required in Summerton. This is not what is being claimed in the present invention. If, as is apparently being suggested by the Examiner, only the concept of a cleavable linker is being extracted from Summerton absent from the other claim elements, Applicants believe this to be improper. Summerton provides no reason or motivation why anyone would "dissect" its method, only utilizing one component and discarding others. To do so would defeat the purpose of Summerton. "A piecemeal reconstruction of the prior art patents in light of the applicant's disclosure shall not be the basis for a holding of obviousness." *In re Rothermel*, 47 CCPA 866, 870, 276 F.2d 393, 396 (1960). Furthermore, it is impermissible to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts

necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art. *In re Wesslau*, 53 CCPA 746, 750, 353 F.2d 238, 241 (1965).

2. The Examiner alleges that inclusion of a cleavable linker in the method of Seligson would result in a more rapid release of nucleic acids. Applicants dispute this theoretical motivation. There is no indication in Summerton that use of a cleavable linker results in more rapid release of nucleic acids. Nor has the Examiner provided any extrinsic evidence of the truth of this statement. Certainly there is no evidence that applying a cleavable linker to the method of Seligson would speed it up. Indeed the only use of the word 'rapid' in Summerton is in connection with a "rapid pairing reagent" or a "rapid capture component". This is distinct from and has nothing to do with the concept of rapid release alleged by the Examiner.

3. The proposed combination of Seligson as modified by Summerton is defective for another reason. The method of Seligson is essentially a column chromatographic separation of nucleic acids from other sample components. Seligson makes clear that the method is conducted by applying a sample to a packed column containing anion exchange packing material and achieving separation by passage of different eluents through one or more columns. Incorporating a cleavable linker as taught by Summerton into the particulate column packing material of Seligson would, at best, lead to a method where the column packing would have to be destroyed in mid-use when the cleavable linker is severed. Yet this is counter to the entire experience of chromatographic technology. Columns are intended for multiple uses; destroying the function of the column mid-use would add greatly to the cost and difficulty of the method and would require repacking columns every time. Additionally, chemically disrupting the composition of the column packing material might well be expected to be detrimental to the physical integrity of the stationary phase and the flow characteristics by producing column void areas or increasing back

pressure. In Applicants' view, one skilled in the art of column chromatographic separations would not be motivated to employ the modification as allegedly taught by Summerton to the column-based method of Seligson. Moreover, it is difficult to see how the problems this modification would cause could provide a "more rapid method".

4. Yet another technical difficulty exists in the proposed modification of Seligson by Summerton. Seligson, in stating the problem to be solved, describes the difficulty of separating nucleic acids from mixtures containing other components including acid mucopolysaccharides. The problem is solved by a two step elution profile in which weakly binding substances are eluted from the column by a first set of conditions and the nucleic acids eluted from the column by a second set of conditions designed to leave other contaminants on the column. Column 3 lines 51-55 of Seligson states:

> Contaminating substances adsorbed under the same conditions as the nucleic acids may thereby be left within the column, e.g., stronger bound contaminants are separated away from the nucleic acids.

Seligson lists among the undesirable contaminants that interfere with nucleic acid hybridization of the isolated nucleic acids, carboxylated mucopolysaccharides and sulfated muco-polysaccharides. Yet the specification of Seligson discloses that sulfated mucopolysaccharides remain bound to the column along with the nucleic acids after a first elution step (see Example I, column 11 lines 19-20 and 25-26 and claim 1). It is only after a second selective elution step that nucleic acids are separated from sulfated mucopolysaccharides. Any step of cleaving a group on the solid phase would prevent the separation of nucleic acids from at least one class of contaminants which the method of Seligson is designed to remove, thus defeating its purpose. Cleaving before the first elution step would allow everything to elute, i.e., no separation. Cleaving before the second elution step would cleave the linker binding both nucleic acids and

sulfated mucopolysaccharides and thereby produce contaminated nucleic acids. Cleaving after the second elution step would be of no effect or utility since the nucleic acid had already been eluted. Thus it can be seen that the proposed combination would not work as proposed by the Examiner; there can be no motivation to combine the references. The proposed modification would destroy the column or change its principle of operation, and therefore is improper. "If the proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification". See MPEP 2143.01 V; and *In re Gordon* 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984). "If the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims prima facie obvious". See MPEP 2143.01 VI; and In re Ratti, 270 F.2d 810, 123 USPQ 349 (CCPA 1959).

In view of the detailed arguments in rebuttal of this ground of rejection, Applicants maintain that no *prima facie* case of obviousness has been established and respectfully request withdrawal of the rejection.

Claims 3-5 and 47 were rejected under 35 USC § 103(a) as being unpatentable over US 4,935,342 to **Seligson** in view of US 6,060,246 to **Summerton** as applied to claims 1-3, 6-12, 19-22, 30, 32-35, 42-46 and 48-50 by the Examiner and further in view of US 6,602,657 to **Bronstein** and US 6,818,454 to **Goshe**. Applicants' above comments and arguments regarding the improper proposed modification of Seligson in view of Summerton are hereby repeated. The addition of Goshe *et al.* does not overcome the deficiencies in the disclosures of Seligson and

Summerton. No *prima facie* case of obviousness has been established. Withdrawal of the rejection is respectfully requested.

Claims 13-15 and 23-29 were rejected under 35 USC § 103(a) as being unpatentable over US 6,060,246 to **Summerton** in view of US 5,707,559 to **Schaap**. Applicants' above comments and arguments regarding the improper proposed modification of Seligson in view of Summerton are hereby repeated. The addition of Schaap *et al.* does not overcome the deficiencies in the disclosures of Seligson and Summerton. No *prima facie* case of obviousness has been established. Withdrawal of the rejection is respectfully requested.

Claims 16 and 17 were rejected under 35 USC § 103(a) as being unpatentable over US 4,935,342 to **Seligson** in view of US 6,060,246 to **Summerton** as applied to claims 1-3, 6-12, 19-22, 30, 32-35, 42-46 and 48-50 by the Examiner and further in view of US 6,514,700 to **Singh**. Applicants' above comments and arguments regarding the improper proposed modification of Seligson in view of Summerton are hereby repeated. The addition of Singh does not overcome the deficiencies in the disclosures of Seligson and Summerton. No *prima facie* case of obviousness has been established. Withdrawal of the rejection is respectfully requested.

Claims 36-37 and 41 were rejected under 35 USC § 103(a) as being unpatentable over US 4,935,342 to **Seligson** in view of US 6,060,246 to **Summerton** as applied to claims 1-3, 6-12, 19-22, 30, 32-35, 42-46 and 48-50 by the Examiner and further in view of **Mukhamedgaliev** *et al.* and further in view of **Reinecke** *et al.* and further in view of US 6,602,657 to **Bronstein** *et al.* and US 6,818,454 to **Goshe** *et al.*. Applicants' above comments and arguments regarding the

improper proposed modification of Seligson in view of Summerton are hereby repeated. The addition of Mukhamedgaliev, Reinecke, Bronstein, and Goshe do not overcome the deficiencies in the disclosures of Seligson and Summerton. No *prima facie* case of obviousness has been established. Withdrawal of the rejection is respectfully requested.

Claim 38-40 were rejected under 35 USC § 103(a) as being unpatentable over US 4,935,342 to **Seligson** in view of US 6,060,246 to **Summerton** as applied to claims 1-3, 6-12, 19-22, 30, 32-35, 42-46 and 48-50 by the Examiner and further in view of **Hughes** *et al.* and further in view of US 4,904,819 to **Hagashita** *et al.*. Applicants' above comments and arguments regarding the improper proposed modification of Seligson in view of Summerton are hereby repeated. The addition of Hughes and Hagashita do not overcome the deficiencies in the disclosures of Seligson and Summerton. No *prima facie* case of obviousness has been established. Withdrawal of the rejection is respectfully requested.

All grounds for rejection having been addressed, and to the best of Applicants' knowledge overcome, Notice of Allowance is respectfully requested.

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